REMARKS

Upon entry of the amendments made herein, claims 1, 37, 39, 40, 42-46, 57, 59, 60 and 62-66 are pending in this application. By this amendment, Applicants have amended claims 1, 39, 40 and 42-46. New claim 66 has been added. Claims 38, 41, 47 and 54 are canceled herein without prejudice or disclaimer. Claims 2-36, 48-53, 55, 56, 58 and 61 were previously canceled.

Claim 1 has been amended to further define the claimed invention. Support for these amendments can be found in the specification and claims as originally filed. Specifically, support can be found, *e.g.*, on page 87, lines 1-23; page 88, lines 3-15 and page 88, line 28 through page 89, line 3 of the specification as filed. Claims 39, 40 and 42-46 have been amended to further define the invention. Support for new claim 66 can be found, *e.g.*, in Table 2 and in original claim 54 of the specification as filed. Accordingly, no new matter has been added.

Enablement

Claims 1, 37-47, 54, 57, 59, 60 and 62-65 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. According to the Examiner, the skilled artisan would have to conduct undue experimentation in order to practice the claimed invention (*see* Final Office Action at p. 8). Specifically, the Examiner alleges that the properties of the compounds of formula (I) are unpredictable (*see* Final Office Action at p. 3). The Examiner further stated that Applicants have not taught the skilled artisan how to determine which tetracycline derivatives are appropriate for treating spinal muscular atrophy (SMA) (*see* Final Office Action at p. 4). In addition, the Examiner noted that the skilled artisan would not be able to recognize if a change in splicing was a successful treatment for SMA because there is no disclosure of successful splicing modulation (*see* Final Office Action at p. 7). Applicants traverse the rejection.

The Examiner highlighted Liu *et al.* (Current Medicinal Chemistry, 2001, 8, pp. 243-252; "Liu") as supporting the notion that the chemical arts are unpredictable. Thus, the Examiner concluded that the scope of formula (I) is too broad to predict a therapeutic effect for the entire claim scope. Applicants disagree. However, in an effort to further prosecution, Applicants have amended the scope of formula (I) to recite compounds where X is $CR^{6'}R^{6}$;

R^4 is $NR^{4'}R^{4''}$; R^3, R^6, $R^{6'}$, R^8, R^9, R^{10}, R^{11} and R^{12} are each H; R^2, $R^{2'}$, $R^{4'}$ and $R^{4''}$ are H or alkyl; and R^7 is substituted alkenyl, substituted alkynyl, substituted phenyl, substituted or unsubstituted furanyl, acyl, or aminoalkyl. Applicants submit that, in view of the arguments made *infra*, the current method for treating SMA comprising the administration of a compound of formula (I) is not unpredictable in view of the instant specification and the knowledge in the art.

Furthermore, the Examiner remarked that Chakkalakal *et al.* (The FASEB Journal, 2005, 19, pp. 880-891; "Chakkalakal") demonstrates the inability of *in vitro* based assays to make absolute predictions about *in vivo* efficacy (*see* Final Office Action at p. 4). However, the legal standard of enablement does not require "absolute predictability." Rather, the standard of enablement considers whether any experimentation needed to practice the invention is undue or unreasonable (*see* MPEP § 2164.01). As discussed *infra*, Applicants assert that any experimentation needed to practice the invention is not undue.

The Examiner also asserted that Andreassi *et al.* (Human Molecular Genetics, 2001, 10(24), pp.2841-2849; "Andreassi") describes tetracycline as showing no activity in altering the splicing of the SMN2 gene. Thus, the Examiner concludes that there is no reason to believe that similar compounds would have the ability to ameliorate SMA in a patient (*see* Final Office Action at p. 5). However, the compounds of formula (I) are 7-substituted derivatives of sancycline. Such 7-substituted sancycline compounds are chemically distinct from tetracycline. Unlike tetracycline, the claimed compounds do not include 6-hydroxyl or 6-methyl groups. Further, unlike tetracycline which is unsubstituted at the 7-position, the claimed compounds are substituted with substituted alkenyl, substituted alkynyl, substituted phenyl, substituted or unsubstituted furanyl, acyl, or aminoalkyl groups at the 7-position. The Examiner has previously stated and currently maintains that chemical modifications lead to unpredictable therapeutic properties. Specifically, the Examiner noted that a single species of a genus would not necessarily predict the therapeutic benefit of the whole genus of compounds (*see* Final Office Action at p. 4). As such, the Examiner's application of Andreassi to the presently claimed compounds is not appropriate as it describes a property of one compound, tetracycline. Further, tetracycline is outside the scope of formula (I). Accordingly, Applicants submit that Andreassi fails to address the therapeutic properties of the compounds of formula (I).

The Examiner also stated that Applicants have not taught the skilled artisan how to determine which tetracycline derivatives are appropriate for treating SMA (*see* Final Office Action at p. 4). However, Andreassi states that "[o]ur results demonstrate the feasibility of identifying by high throughput screens other compounds and/or aclarubicin derivatives that increase full-length mRNA production and SMN protein from the SMN2 gene" (*see* Andreassi at p. 4, second paragraph). According to Andreassi, the identification of compounds useful for the treatment of SMA is reasonable and, as such, is within the skill of the ordinary artisan to determine by routine experiment.

Zhang *et al.* (Gene Therapy, 2001, 8, pp. 1532-1538; "Zhang") also describe a method of screening compounds which modify SMN2 splicing (courtesy copy included herewith). Specifically, Zhang concludes that the results described therein "demonstrate that this system can be utilized to identify small molecules that regulate the splicing of SMN exon 7" (*see* Zhang at p.1532 (abstract)). Andreassi and Zhang describe the state of the art, which includes the identification of compounds useful for the treatment of SMA. Thus, such screening is experimentation which is routine in the art.

Further, as stated in Applicants' previous response filed on September 8, 2009, Applicants have described methods for identifying tetracycline compounds for treating SMA (*see e.g.*, page 11, lines 8-19 of the specification as originally filed). Such methods include measuring the ability of a tetracycline compound to modulate RNA and comparing experimental results for a number of tetracycline compounds to identify those having superior properties for the treatment of SMA.

In accordance with Andreassi and Zhang, the instant specification teaches methods for identifying compounds for the treatment of SMA. Thus, contrary to the Examiner's assertion, Applicants assert that a skilled artisan could determine which tetracycline derivatives are appropriate for treating SMA in view of the present application and the knowledge in the art.

The Examiner argued that the skilled artisan would not be able to recognize if a change in splicing was a successful treatment for SMA because there is no disclosure of successful splicing modulation (*see* Final Office Action at p. 7). It is well understood that a specification need not rewrite what is known in the art. MPEP 2164.05(a) states that "[t]he specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public." It is

known in the art that SMA treatment is effective where the SMN2 mRNA is modulated to include exon 7:

Zhang describes a system for the *in vivo* screening of compounds that promote such exon 7 inclusion (*see* Zhang at p. 1537);

Andreassi describes that gene therapy resulting in exon 7 inclusion in SMN2 mRNA can successfully treat SMA (*see* Andreassi at p. 4).

Thus, the skilled artisan would be able to recognize if a particular splicing modulation is useful as a treatment for SMA.

The Examiner stated that Applicants have not taught one of skill in the art how to identify which tetracycline compounds would be able to overcome known obstacles in the art, such as those described by Andreassi (*see* Final Office Action at p. 8). Each of the "obstacles" described by the Examiner is addressed *supra*, and solutions are provided either by the specification as filed or in the art.

The Examiner further alleged that the art provides strong evidence suggesting that tetracycline-based compounds do not function to alter the splicing of SMN2 or to treat SMA (*see* Final Office Action at p. 6). Thus, the Examiner concludes that a lack of any working examples supports a finding of non-enablement (*see* Final Office Action at p. 7).

As the Examiner acknowledged, Chapter 2164.02 of the MPEP states that "[c]ompliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." "The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)." As discussed *supra*, the art is abundant with routine assays to assess the claimed compounds' efficacy in altering the splicing of SMN2 or treating SMA.

Further, Andreassi describes a tetracycline compound whose structure is chemically distinct from the claimed compounds of formula (I), as described above. The Examiner has acknowledged that chemical modifications lead to unpredictable therapeutic properties. Thus, Andreassi does not provide sufficient evidence, much less strong evidence, that all tetracycline-based compounds (including those currently claimed) are ineffective at treating SMA. Further, the Examiner has previously described Hertweck *et al.* (Eur. J. Biochem., 2002, 269, pp. 175-183; "Hertweck") as providing an example of a tetracycline derivative

(*i.e.*, 7-chlorotetracycline) capable of inhibiting, rather than promoting, splicing of nuclear RNA (*see* Office Action dated May 6, 2009 at p. 12). However, as with tetracycline, this derivative is chemically distinct from the claimed species and, thus, Hertweck does not provide sufficient evidence, much less strong evidence, that all tetracycline-based compounds (including those 7-substituted sancycline compounds currently claimed) are ineffective at treating SMA. Therefore, in view of the instant specification and the art as described above, the claimed invention is enabled.

In view of the above, Applicants submit that the art typically or routinely engages in the experimentation described throughout the specification and claims. Thus, based on Applicants' disclosure and the knowledge in the art, one of ordinary skill would be able to practice the claimed invention without undue experimentation. Accordingly, Applicants submit that the enablement rejection has been overcome and should be withdrawn.

CONCLUSION

Applicants respectfully submit that this application is in condition for allowance. If there are any questions regarding this amendment and/or these remarks, the Examiner is respectfully requested to telephone the Applicants' attorney undersigned.

Respectfully submitted,

Heidi A. Erlacher, Reg. No. 45,409
Christopher E. Olson, Reg. No. 55,510
Attorneys for Applicants
c/o MINTZ LEVIN
Telephone: (617) 542-6000
Facsimile: (617) 542-2241
Customer Number 30623

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